09/851,422

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L1	lytic peptide	505	L1

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L3: Entry 16 of 24 File: USPT Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968904 A
TITLE: Modified arginine containing lytic peptides and method of making the same by glyoxylation

Abstract Text (1):
A non-neurotoxin, arginine residue-containing non-naturally occurring lytic peptide comprising a sequence of amino acid residues in sufficient number and arrangement to confer lytic activity to the peptide, wherein the guanido groups of the arginine residues and the .alpha.-amino group of the N-terminal amino acid are sufficiently glyoxylated to impart enhanced tryptic, chymotryptic, and aminopeptidase digestion resistance to the peptide. The compositions of the invention are suitable for in vivo administration. A method of-making the same, to impart enhanced tryptic digestion resistance thereto, comprising glyoxylating the guanido groups of the arginine residues and the .alpha.-- amino group of the N-terminal amino acid with glyoxa containing buffer for sufficient time and at sufficient conditions to glyoxylate the side chain and .alpha.-amino groups to sufficient extent to confer enhanced proteolytic digestion resistance to the peptide.

Brief Summary Text (3):
The present invention relates to glyoxylation-stabilized, arginine-containing synthetic lytic peptide compositions with enhanced resistance to proteolytic digestion, and to methods of making the same.

Brief Summary Text (5):
Naturally occurring amphipathic lytic peptides play an important if not critical role as immunological agents in insects and have some, albeit secondary, defense functions in a range of other animals. The function of these peptides is to destroy prokaryotic and other non-host cells by disrupting the cell membrane and promoting cell lysis. Common features of these naturally occurring amphipathic, lytic peptides include an overall basic charge, a small size (23-39 amino acid residues), and the ability to form amphipathic .alpha.-helices. Several types of amphipathic lytic peptides have been identified: cecropins (described in U.S. Pat. Nos. 4,355,104 and 4,520,016 to Hultmark et al.), defensins, sarcotoxins, melittin, and magainins (described in U.S. Pat. No. 4,810,777 to Zasloff). Each of these peptide types is distinguished by sequence and secondary structure characteristics.

Brief Summary Text (6):
Several hypotheses have been suggested for the mechanism of action of the lytic peptides: disruption of the membrane lipid bilayer by the amphipathic .alpha.-helix portion of the lytic peptide; lytic peptide formation of ion channels, which results in osmotically induced cytolysis; lytic peptide promotion of protein aggregation, which results in ion channel formation; and lytic peptide-induced release of phospholipids. Whatever the mechanism of lytic peptide-induced membrane damage, an ordered secondary conformation such as an .alpha.-amphipathic helix and positive charge density are features that appear to participate in the function of the lytic peptides.

Brief Summary Text (7):
Active analogs of naturally occurring lytic peptides have been produced and tested in vitro against a variety of prokaryotic and eukaryotic cell types (see for example Arrowood, M. J., et al. J. Protozool. 38: 161s [1991]; Jaynes, J. M., et al. FASEB J. 2: 2878 [1988]), including: gram positive and gram negative bacteria, fungi, yeast, envelope viruses, virus-infected eukaryotic cells, and neoplastic or transformed mammalian cells. The results from these studies indicate that many of the synthetic lytic peptide analogs have similar or higher levels of lytic activity for many different types of cells, compared to the naturally occurring forms. In addition, the peptide concentration required to lyse microbial pathogens such as-protozoans, yeast, and bacteria does not lyse normal mammalian cells.

Brief Summary Text (8):
The specificity of the lytic action depends upon the sequence and structure of the peptide, the concentration of the peptide, and the type of membrane with which it interacts. Jaynes et aL Peptide Research 2: 157 (1989) discuss the altered cytoskeletal characteristics of transformed or neoplastic mammalian cells that make them susceptible to lysis by the peptides. In these experiments, normal, human non-transformed cells remained unaffected at a given peptide concentration while transformed cells were lysed; however, when normal cells were treated with the cytoskeletal inhibitors cytochalasin D or colchicine, sensitivity to

lysis increased. The experiments show that the action of lytic peptides on normal mammalian cells is limited. This resistance to lysis was most probably due to the well-developed cytoskeletal network of normal cells. In contrast, transformed cell lines which have well-known cytoskeletal deficiencies were sensitive to lysis. Because of differences in cellular sensitivity to lysis, amphipathic peptide concentration can be manipulated to effect lysis of one cell type but not another at the same locus.

Brief Summary Text (9):
Synthetic lytic peptide analogs can also act as agents of eukaryotic cell proliferation. Peptides that promote lysis of transformed cells will, at lower concentrations. promote cell proliferation in some cell types. This stimulatory activity is thought to depend on the channel-forming capability of the peptides, which somehow stimulates nutrient uptake, calcium influx or metabolite release, thereby stimulating cell proliferation (see Jaynes, J. M. Drug News & Perspectives 3: 69 [1990]; and Reed, W. A. et al. Molecular Reproduction and Development 31: 106 [1992]). Thus, at a given concentration, these peptides stimulate or create channels that can be beneficial to the normal mammalian cell in a benign environment where it is not important to exclude toxic compounds.

Brief Summary Text (10):
The synthetic lytic peptide analogs typically contain as few as 12 and as many as 40 amino acid residues. A phenylalanine residue is often positioned at the amino terminus of the protein to provide an aromatic moiety analogous to the tryptophan residue located near the amino terminus of natural cecropins and a UV-absorbing moiety with which to monitor the purification of the synthetic peptide. The basis for the design of these lytic peptide analogs is that an amphipathic peptide of minimal length and containing overall positive charge density effects lytic activity. Peptides that have the structural motif of a .beta.-pleated sheet and overall positive charge density can also effect lytic activity.

Brief Summary Text (11):
As discussed in the preceding paragraph, in vitro laboratory tests of the lytic peptide analogs have been successful. However, the use of the lytic peptide analogs in vivo could be considerably limited in circumstances where proteases may digest the peptide analogs before sufficient pathogen cell lysis has occurred. In particular, the high concentration of positively charged amino acids such as lysine and arginine make the synthetic peptides susceptible to tryptic digestion. The secondary conformation of the peptides sequesters the hydrophobic amino acid residues, thus shielding them from interaction with proteases such as chymotrypsin, which hydrolyzes peptides at bulky or aromatic amino acid residues. This proteolytic susceptibility is a general problem for peptides and proteins when used in vivo. Many techniques are suitable for stabilizing proteins for in vitro use but are not appropriate for in vivo or oral administration to humans and animals.

Brief Summary Text (15):
Accordingly, it would be a significant advance in the art to provide a method of producing chemically modified physiologically active lytic peptides that have enhanced resistance to proteolysis.

Brief Summary Text (19):
The present invention relates generally to glyoxylation-stabilized, arginine-containing synthetic lytic peptide compositions, and to methods of making the same.

Brief Summary Text (22):
The invention relates in a further aspect to a physiologically active peptide composition comprising a physiologically active synthetic peptide that has been chemically modified, wherein the .epsilon.-amino group of the lysine residue and the .alpha.-amino group of the N-terminal amino acid have been first been methylated, and the side chain of the arginine residues are subsequently glyoxylated such that the chemically modified physiologically active peptide has enhanced in vivo resistance to proteolytic digestion, relative to the physiologically active peptide alone.

Brief Summary Text (35):
Chemical modification of lytic peptide analogs offers certain advantages. If the modifications are made in such a way that the lytic peptides retain all or most of their biological activity, then the following advantage results: the peptides have enhanced stability to proteolysis. With enhanced stability, the peptides can be administered in vivo without loss of biological activity through proteolytic digestion.

Brief Summary Text (36):
When considering lytic peptide analog stabilization with chemical modification of amino acid residue side chains, it is important to consider the character (hydrophobic or hydrophilic) and location of the individual amino acids residues within the peptides of concern. With the lytic peptide analogs proposed herein, the following are the only types of amino acid residues to be examined: phenyalanine, alanine, aspartate, valine, isoleucine, leucine, glycine, lysine, and arginine. Of this group, lysine, arginine and aspartate are potentially exposed to proteases in the aqueous environment, as a result of the secondary conformation of the peptide. In peptides containing aspartate. this group could be previously chemically modified to mask the amino acid residue. The .epsilon.-amino groups of the lysine residues would be also previously methylated to mask the lysine side chains.

Brief Summary Text (37):
The lytic peptide analogs are designed to take the configuration of an amphipathic .alpha.-helix structure or a .beta.-pleated sheet conformation. In an aqueous environment the hydrophobic regions of these peptides would adhere to each other, forming micelles and hence isolated domains of a separate phase. In this circumstance, the hydrophobic moieties would be unavailable to the aqueous phase and hence to hydrolysis by proteolytic enzymes. In one preferred aspect of the invention, the lytic peptides assume the secondary conformation of an amphipathic .alpha.-helix.

Brief Summary Text (38):
Each arginine side chain contains a side chain guanido group which provides the peptide, at physiological pH with a unit positive charge. The combined multiple charge of each arginine guanido group contributes to the polarity and thus the regional hydrophilicity required for formation of an amphipathic .alpha.-helix. The positive charge of these lytic peptide analogs is required for activity. Amphipathy alone does not provide for lytic action. Modification of the side chain group of the arginine amino acid residue does not affect the unit charge of the arginine residue or the peptide. However, susceptibility to tryptic hydrolysis for the arginine residue .alpha.-carbonyl peptide linkages is drastically reduced.

Brief Summary Text (39):
As discussed above, it can be presumed that alanine, valine, leucine, isoleucine, glycine, internal phenylalanine, aspartate, and lysine residues contained in the lytic peptide analogs are not vulnerable to proteolytic attack due to their removal from the aqueous phase or prior chemical masking. Arginine. however, provides a specific locus for the most aggressive proteolytic enzyme, trypsin. For this reason, glyoxylation of the lytic peptides would provide enhanced stability to proteolytic hydrolysis. It should also be noted that the N-terminal .alpha.-amino group is also exposed and would also become glyoxylated during such a procedure unless the peptide was subjected to prior methylation, thus providing further resistance to both chymotrypsin, which attacks aromatic amino acids such as phenylalanine, and aminopeptidases, which act at the N-terminus.

Brief Summary Text (40):
One objective of the present invention is to provide enhanced proteolytic stability to a series of arginine-containing, lytic peptide analogs. Another objective is to use such modified lytic peptides for in vivo delivery of physiologically effective lytic peptides.

Detailed Description Text (3):
Representative Lytic Peptides

Detailed Description Text (5):
Chemicals modification of lytic peptide analogs offers certain advantages. If the modifications are made in such a way that the peptides retain all or most of their lytic characteristics, then physiologically active peptides have enhanced stability to proteolyisis. With enhanced stability, oral delivery of the peptide is advantageously accomodated without excessive loss of activity due to proteolytic digestion.

Detailed Description Text (8):
An exemplary and preferred reaction scheme for glyoxylation of the guanido groups of arginine residues and the N-terminal .alpha.-amino acid in a representative lytic peptide is describe below.

Detailed Description Text (23):
The effect of two lytic peptides, SEQ ID NO. 14 and DP-1 (a mellitin analog) were tested against pathogenic bacteria in vitro. DP-1 is a convenient test 23-mer lytic peptide with the sequence
Phe-Ala-Leu-Ala-Leu-Lys-Ala-Leu-Lys-Lys-Ala-Leu-Lys-Lys-Leu-Lys-Lys-Ala-Le u-Lys-Lys-Ala-Leu. In this test, antibiotic resistant clinical isolates of Pseudomonas aeruginosa and Staphylococcus aureus were obtained. The lytic peptide bioassay was performed as described below.

Other Reference Publication (5):
Jaynes et al., "In Vitro Cytocidal Effect of Lytic Peptides . . . Cell Lines" Peptide Research, 2:157-160 (1989).

Other Reference Publication (6):
Jaynes, "Lytic Peptides Portend an Innovative Age in the Management . . . Human Disease", Drug News & Perspective, 3:69-78 (1990).

Other Reference Publication (9):
Arrowood et al., "Hemolytic Properties of Lytic Peptides Active . . . Cryptosporidium Parvum", J. Protozool., 38:161S-163S (1991).

Other Reference Publication (10):

Jaynes et al., "In vitro cytocidal effect of novel lytic peptides on . . . Trypanosoma cruzi", Faseb J., 2:2878-2883 (1988).

Other Reference Publication (11):
Graham et al., "Cytoxic Effect of Amphipathic Cationic Lytic Peptides on . . . Lines", Proc. of Amer. Assoc. for Cancer Res., 35:410 (1994).

CLAIMS:

1. A non-neurotoxin, arginine residue-containing lytic peptide of enhanced tryptic digestion resistance, comprising glyoxylated guanido groups on the arginine residues.

2. A peptide of claim 1 wherein the peptide is a non-naturally occurring .alpha.-helical amphipathic lytic peptide.

3. A peptide of claim 1 wherein the peptide is a non-naturally occurring .beta.-pleated sheet lytic peptide.

5. A non-neurotoxin, arginine residue-containing peptide according to claim 1 wherein the peptide is a non-naturally occurring lytic peptide wherein the .epsilon.-amino groups on the lysine residues and the .alpha.-amino group of the N-terminal amino acid residue are methylated.

8. A non-neurotoxin, arginine residue-containing peptide according to claim 1 wherein the lytic peptide has the .alpha.-amino group of the N-terminal amino acid residue sufficiently glyoxylated in order to enhance resistance of the peptide to aminopeptidase digestion, in addition to tryptic digestion.

2/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0002725274 BIOSIS NO.: 197968036773
COMPARISON OF THE BIOSYNTHESIS AND RELEASE OF LUTEINIZING HORMONE BY RAT PITUITARIES IN-VITRO IN RESPONSE TO GONADOTROPIN RELEASING HORMONE ANALOGS
AUTHOR: LIU T-C (Reprint); JACKSON G L
AUTHOR ADDRESS: DEP VET BIOSCI, COLL VET MED, 261 VET MED BUILD, URBANA, ILL 61801, USA**USA
JOURNAL: Endocrinology 104 (4): p962-966 1979
ISSN: 0013-7227
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In an attempt to determine whether gonadotropin-releasing hormone (GnRH) regulates synthesis and release of LH [luteinizing hormone] via independent processes, the ability of several GnRH analogs to regulate LH release was compared with their ability to regulate LH synthesis. Pituitary glands from ovariectomized rats were incubated with [3H]glucosamine in the presence of increasing doses of either GnRH or GnRH agonists: (des-Gly-NH210)GnRH ethylamide, (D-Ala6, des-Gly-NH210)GnRH ethylamide, or (D-Lys6, . **epsilon** .- **polyglutamate**)GnRH. After incubation, total immunoreactive LH (IR-LH) was measured by RIA [radioimmunoassay] and radiolabeled LH was measured by immunoprecipitation with specific anti-LH.beta. serum. The dose-response curves for synthesis (medium plus tissue) of [3H]glucosamine-labeled LH ([3H]LH) were similar to those for release. The dose required for half-maximal stimulation of release (KmR) of [3H]LH differed from the dose required for half-maximal stimulation of synthesis (KmS) of [3H]LH for GnRH and all agonists. The ratio of KmR to KmS for [3H]LH ranges from 0.75-1.98. The ratio of KmR for IR-LH to KmS for [3H]LH ranged from 1.4-4.3. Addition of the antagonist (des-His2, D-Ala6)GnRH to the incubation system inhibited GnRH-induced synthesis of [3H]LH and release of [3H]LH and IR-LH. The dose required for half-maximal inhibition of GnRH-induced release of either IR-LH or [3H]LH was 0.4 times that required for half-maximal inhibition of synthesis. Comparison of the medium to tissue ratios of IR-LH and [3H]LH in response to increasing doses of GnRH or agonists revealed that the dose per se affected the relative rates of release of both [3H]LH and IR-LH. GnRH analogs have similar effects on LH synthesis and release; the doses of GnRH analogs required for half-maximal stimulation of LH synthesis are lower than those required for half-maximal stimulation of release; the dose of GnRH regulates relative rates of release vs. synthesis of LH and the dose of GnRH regulates relative rates of release of newly synthesized vs. stored LH.

REGISTRY NUMBERS: 9002-67-9: LUTEINIZING HORMONE; 56-41-7Q: ALANINE; 302-72-7Q: ALANINE; 56-87-1Q: LYSINE; 70-54-2Q: LYSINE; 11070-68-1: GLUTAMATE; 3416-24-8: GLUCOSAMINE
DESCRIPTORS: 2 DEHISTIDINE 6-D ALANINE GONADOTROPIN RELEASING HORMONE 10 DEGLYCINAMIDE GONADOTROPIN RELEASING HORMONE ETHYLAMIDE 6-D ALANINE 10 DEGLYCINAMIDE GONADOTROPIN RELEASING HORMONE ETHYLAMIDE 6-D LYSINE **EPSILON** POLY GLUTAMATE GONADOTROPIN RELEASING HORMONE HORMONE-DRUG GLUCOSAMINE
DESCRIPTORS:
MAJOR CONCEPTS: Endocrine System--Chemical Coordination and Homeostasis; Metabolism; Pharmacology
BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
COMMON TAXONOMIC TERMS: Animals; Chordates; Mammals; Nonhuman Vertebrates ; Nonhuman Mammals; Rodents; Vertebrates
CHEMICALS & BIOCHEMICALS: LUTEINIZING HORMONE; ALANINE; ALANINE; LYSINE ; LYSINE; GLUTAMATE; GLUCOSAMINE

2/9/3 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07522076 92385806 PMID: 1381235

Defective transport as a mechanism of acquired resistance to methotrexate in patients with acute lymphocytic leukemia.

Trippett T; Schlemmer S; Elisseyeff Y; Goker E; Wachter M; Steinherz P; Tan C; Berman E; Wright J E; Rosowsky A; et al

Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.

Blood (UNITED STATES) Sep 1 1992, 80 (5) p1158-62, ISSN 0006-4971 Journal Code: 7603509

Contract/Grant No.: CA 19589; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: AIM; INDEX MEDICUS

Although the mechanisms of resistance to methotrexate (MTX) are known in experimental tumors made resistant to this drug, little information is available regarding acquired resistance to MTX in patients. A competitive displacement assay using the fluorescent lysine analogue of MTX, N-(4-amino-4-deoxy-N10-methylpteroyl)-N **epsilon** -(4'-fluorescein-thiocarbamyl)-L-lysine (PT430), was developed as a sensitive method of detection of transport resistance to MTX in cell lines, as well as in blast cells from patients with leukemia. Rapid uptake of PT430 at high concentrations (20 mumol/L) in leukemic blasts resulted in achievement of steady-state levels within 2 hours. Subsequent incubation with the folate antagonists, MTX and trimetrexate (TMTX), which differ in the mode of carrier transport, produced characteristic patterns of PT430 displacement. Flow cytometric analysis of the mean fluorescence intensity in the human CCRF-CEM T-cell lymphoblastic leukemia cell line and its MTX-resistant subline clearly identified the presence of transport deficiency in the resistant subline. Analysis of blasts from 17 patients with leukemia, nine with no prior chemotherapy and eight previously treated with chemotherapy, found evidence of MTX transport resistance in two of the four patients who were treated with MTX and considered to be clinically resistant to the drug. The finding that blast cells of some patients with leukemia considered clinically resistant to MTX is due to decreased MTX transport has important implications for clinical use of this drug and for new drug development.

Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Descriptors: *Leukemia, Lymphocytic, Acute--drug therapy--DT; *Methotrexate--pharmacokinetics--PK; Adolescent; Adult; Aged; Biological Transport; Child; Child, Preschool; Drug Resistance; Infant; Leukemia, Lymphocytic, Acute--metabolism--ME; Methotrexate--analogs and derivatives --AA; Methotrexate--metabolism--ME; Methotrexate--therapeutic use--TU; Middle Age; Polyglutamic Acid--analogs and derivatives--AA; Polyglutamic Acid--metabolism--ME; Trimetrexate--pharmacokinetics--PK; Tumor Cells, Cultured

CAS Registry No.: 25513-46-6 (Polyglutamic Acid); 52128-35-5 (Trimetrexate); 59-05-2 (Methotrexate); 82334-40-5 (methotrexate polyglutamate)

Record Date Created: 19921006

Record Date Completed: 19921006

8/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02726175 BIOSIS NO.: 000068036773
COMPARISON OF THE BIOSYNTHESIS AND RELEASE OF LUTEINIZING HORMONE BY RAT PITUITARIES IN-VITRO IN RESPONSE TO GONADOTROPIN RELEASING HORMONE ANALOGS
AUTHOR: LIU T-C; JACKSON G L
AUTHOR ADDRESS: DEP. VET. BIOSCI., COLL. VET. MED., 261 VET. MED. BUILD., URBANA, ILL. 61801, USA.
JOURNAL: ENDOCRINOLOGY 104 (4). 1979. 962-966: 1979
FULL JOURNAL NAME: Endocrinology
CODEN: ENDOA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In an attempt to determine whether gonadotropin-releasing hormone (GnRH) regulates synthesis and release of LH [luteinizing hormone] via independent processes, the ability of several GnRH analogs to regulate LH release was compared with their ability to regulate LH synthesis. Pituitary glands from ovariectomized rats were incubated with [3H]glucosamine in the presence of increasing doses of either GnRH or GnRH agonists: (des-Gly-NH210)GnRH ethylamide, (D-Ala6, des-Gly-NH210)GnRH ethylamide, or (D-Lys6, . **epsilon** .- **polyglutamate**)GnRH. After incubation, total immunoreactive LH (IR-LH) was measured by RIA [radioimmunoassay] and radiolabeled LH was measured by immunoprecipitation with specific anti-LH.beta. serum. The dose-response curves for synthesis (medium plus tissue) of [3H]glucosamine-labeled LH ([3H]LH) were similar to those for release. The dose required for half-maximal stimulation of release (KmR) of [3H]LH differed from the dose required for half-maximal stimulation of synthesis (KmS) of [3H]LH for GnRH and all agonists. The ratio of KmR to KmS for [3H]LH ranges from 0.75-1.98. The ratio of KmR for IR-LH to KmS for [3H]LH ranged from 1.4-4.3. Addition of the antagonist (des-His2, D-Ala6)GnRH to the incubation system inhibited GnRH-induced synthesis of [3H]LH and release of [3H]LH and IR-LH. The dose required for half-maximal inhibition of GnRH-induced release of either IR-LH or [3H]LH was 0.4 times that required for half-maximal inhibition of synthesis. Comparison of the medium to tissue ratios of IR-LH and [3H]LH in response to increasing doses of GnRH or agonists revealed that the dose per se affected the relative rates of release of both [3H]LH and IR-LH. GnRH analogs have similar effects on LH synthesis and release; the doses of GnRH analogs required for half-maximal stimulation of LH synthesis are lower than those required for half-maximal stimulation of release; the dose of GnRH regulates relative rates of release vs. synthesis of LH and the dose of GnRH regulates relative rates of release of newly synthesized vs. stored LH.

DESCRIPTORS: 2 DEHISTIDINE 6-D ALANINE GONADOTROPIN RELEASING HORMONE 10 DEGLYCINAMIDE GONADOTROPIN RELEASING HORMONE ETHYLAMIDE 6-D ALANINE 10 DEGLYCINAMIDE GONADOTROPIN RELEASING HORMONE ETHYLAMIDE 6-D **LYSINE EPSILON** POLY GLUTAMATE GONADOTROPIN RELEASING HORMONE HORMONE-DRUG GLUCOSAMINE

8/9/2 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07522076 92385806 PMID: 1381235
Defective transport as a mechanism of acquired resistance to methotrexate in patients with acute lymphocytic leukemia.
Trippett T; Schlemmer S; Elisseyeff Y; Goker E; Wachter M; Steinherz P; Tan C; Berman E; Wright J E; Rosowsky A; et al
Program of Molecular Pharmacology and Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
Blood (UNITED STATES) Sep 1 1992, 80 (5) p1158-62, ISSN 0006-4971 Journal Code: 7603509
Contract/Grant No.: CA 19589; CA; NCI
Document type: Journal Article

Languages: ENGLISH
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CAS Registry No.: 25513-46-6 (Polyglutamic Acid); 52128-35-5 (Trimetrexate); 59-05-2 (Methotrexate); 82334-40-5 (methotrexate polyglutamate)

09/851,422

Set	Items	Description
S1	0	LYTIC(W)PETIDE?
S2	22871	LYTIC
S3	146739	CYTOTOXIC
S4	7993	(S1 OR S2) AND (PEPTIDE? OR PROTEIN?)
S5	47040	(S2 OR S3) AND (PEPTIDE? OR PROTEIN?)
S6	191	S5 AND EPSILON
S7	30	S6 AND LYSINE
S8	0	S7 AND PEPTIDE(W)BOND?
S9	30	S7
S10	21	RD (unique items)

10/9/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08069147 BIOSIS NO.: 000093090595
ANALOGUES OF LUTEINIZING HORMONE-RELEASING HORMONE CONTAINING CYTOTOXIC **GROUPS**
AUTHOR: JANAKY T; JUHASZ A; BAJUSZ S; CSERNUS V; SRKALOVIC G; BOKSER L; MILOVANOVIC S; REDDING T W; REKASI Z; NAGY A; SCHALLY A V
AUTHOR ADDRESS: DEP. MED. CHEM., ALBERT SZENT-GYORGYI UNIVERSITY MED. SCH., 6720 SZEGED, DOM TER 8, HUNGARY.
JOURNAL: PROC NATL ACAD SCI U S A 89 (3). 1992. 972-976. 1992
FULL JOURNAL NAME: Proceedings of the National Academy of Sciences of the United States of America
CODEN: PNASA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In an attempt to produce better **cytotoxic** analogues, chemotherapeutic antineoplastic radicals including an alkylating nitrogen mustard derivative of D-phenylalanine (D-melphan), reactive cyclopropane, anthraquinone derivatives [2-(hydroxymethyl)anthraquinone and the anticancer antibiotic doxorubicin], and an antimetabolite (methotrexate) were coupled to suitably modified agonists and antagonists of luetinizing hormone-releasing hormone (LH-RH). Analogues with D-lysine6 and D-ornithine6or N. **epsilon** .-(2,3-diaminopropionyl)-D- **lysine** and N.delta.-(2,3-diaminopropionyl)-D-ornithine were used as carriers for one or two **cytotoxic** moieties. The enhanced biological activities produced by the incorporation of D amino acids into position 6 of the agonistic analogues were further increased by the attachment of hydrophobic **cytotoxic** groups, resulting in compounds with 10-50 times higher activity than LH-RH. Most of the monosubstituted agonistic analogues showed high affinities for the membrane receptors of human breast cancer cells, while the receptor binding affinities of the **peptides** containing two **cytotoxic** side chains were lower. Antagonistic carriers [Ac-D-Nal(2)1,D-Phe(4Cl)2,D-Trp3,Arg5,D-Lys6,D-Ala10]LH-RH [where Nal(2) is 3-(2-naphthyl)alanine], [Ac-D-Nal(2)1,D-Phe(4Cl)2,D-Trp3,Arg5,N. **epsilon** .-(2,3-diaminopropionyl)-D-Lys6,D-Ala10]LH-RH, and their D-Pal(3)3 homologs [Pal(3) is 3-(3-pyridyl)alanine] as well as [Ac-D-Nal(2)1,D-Phe(4Cl)2,D-Pal(3)3,Tyr5,N. **epsilon** .-(2,3-diaminopropionyl)-D-Lys6,D-Ala10]LH-RH were linked to **cytotoxic** compounds. The hybrid molecules inhibited ovulation in rats at doses of 10 .mu.g and suppressed LH release in vitro. The receptor binding of **cytotoxic** analogues was decreased compared to the precursor **peptides** , although analogues with 2-(hydroxymethyl)anthroquinone hemiglutarate had high affinities. All of the **cytotoxic** analogues tested inhibited [3H]thymidine incorporation into DNA in cultures of human breast and prostate cancer cell lines. Some **cytotoxic** analogues also significantly suppressed the growth of mammary and prostate cancers in vivo in animal models.

10/9/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06789346 BIOSIS NO.: 000088098783
HIGHLY POTENT METALLOPEPTIDE ANALOGUES OF LHRH
AUTHOR: BAJUSZ S; JANAKY T; CSERNUS V J; BOKSER L; FEKETE M; SRKALOVIC G; REDDING T W; SCHALLY A V

AUTHOR ADDRESS: INST. DRUG RES., P.O. BOX 82, H-1325 BUDAPEST, HUNGARY.
JOURNAL: PROC NATL ACAD SCI U S A 86 (16). 1989. 6313-6317. 1989
FULL JOURNAL NAME: Proceedings of the National Academy of Sciences of the United States of America
CODEN: PNASA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Metal complexes related to the **cytotoxic** complexes cisplatin [cis-diamminedichloroplatinum(II)] and trans-bis(salicylaldoximato)copper(II) were incorporated into suitably modified luteinizing hormone-releasing hormone (LH-RH) analogues containing D- **lysine** at position 6. Some of the metallopeptides thus obtained proved to be highly active LH-RH agonists or antagonists. For instance, SB-40, a PtCl2-containing metallopeptide in which platinum is coordinated to an N-. **epsilon** .-(DL-2,3-diaminopropionyl)-D- **lysine** residue [D-Lys(DL-A2pr)] at position 6, showed 50 times higher LH-releasing potency than the native hormone. SB-95, [Ac-D-Nal(2)1,D-Phe(pCl)2,D-Pal(3)2,Arg5,D-Lys{DL-A2pr(Sal2Cu)}6, D-Ala10]LH-RH, where Nal(2) is 3-(2-naphthyl)alanine, Pal(3) is 3-(3-pyridyl)alanine, and copper(II) is coordinated to the salicylideneimino moieties resulting from condensation of salicylaldehyde with D-Lys(DL-A2pr)6, caused 100% inhibition of ovulation at a dose of 3 .mu.g in rats. Most metallopeptide analogues of LH-RH showed high affinities for the membrane receptors of rat pituitary and human breast cancer cells. Some of these metallopeptides had **cytotoxic** activity against human breast cancer and prostate cancer cell lines in vitro (this will be the subject of a separate paper on cytotoxicity evaluation). Such cytostatic metallopeptides could be envisioned as targeted chemotherapeutic agents in cancers that contain receptors for LH-RH-like **peptides** .

10/9/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02943488 BIOSIS NO.: 000069051606
ENZYMIC LYSIS AND STRUCTURE OF THE CELL WALLS OF THE ORAL STREPTOCOCCUS-MUTANS BHT
AUTHOR: INOUE M; HAMADA S; KOTANI S; KATO K
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JOURNAL: ARCH ORAL BIOL 24 (7). 1979. 529-538. 1979
FULL JOURNAL NAME: Archives of Oral Biology
CODEN: AOBIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Solubilization of purified S. mutans BHT cell walls by Flavobacterium L-11 cell-wall **lytic** enzyme preparation was accompanied by the exposure of 0.92 mol of N-terminal LL-alanine and 0.31 mol of C-terminal D-alanine/mol of glutamic acid residues. No other terminal amino acids and soluble reducing groups were exposed during cell wall lysis. A small but significant amount (0.23 mol) of free L-alanine was liberated by aminopeptidase activity of this enzyme preparation. About 60% of N-acetylmuramyl-L-alanine linkages and 30% of D-alanyl-L-alanine linkages of cell wall peptidoglycan apparently were cleaved by amidase and endopeptidase activities of the cell wall **lytic** enzyme preparation, respectively. Penta-and hexapeptide fractions consisting of glutamic acid, alanine and **lysine** in molar ratio of 1.0:3.0-4.0:1.0 were isolated chromatographically from the cell wall digests. Analyses of N- and C-terminal amino acids suggested that the major **peptides** isolated have the chemical structures of N.alpha.-(L-alanyl-D-isoglutaminyl)-N. **epsilon** .-(L-alanyl)1-2-L-lysyl-D-alanine or N.alpha.-(L-alanyl-D-isoglutaminyl)-N. **epsilon** .-(L-alanyl)2-3-L- **lysine** . A possible structure of peptidoglycan of the cell walls was proposed.

10/9/20 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08362575 95050547 PMID: 7961711

Antiproliferative effects of inhibitors of deoxyhypusine synthase. Inhibition of growth of Chinese hamster ovary cells by guanyl diamines.

Park M H; Wolff E C; Lee Y B; Folk J E

Enzyme Chemistry Section, NIDR, National Institutes of Health, Bethesda, Maryland 20892.

Journal of biological chemistry (UNITED STATES) Nov 11 1994, 269 (45) p27827-32, ISSN 0021-9258 Journal Code: 2985121R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

Certain guanyl diamines are effective inhibitors of deoxyhypusine synthase (Jakus, J., Wolff, E. C., Park, M. H., and Folk, J. E. (1993) J. Biol. Chem. 268, 13151-13159), the first enzyme involved in the biosynthesis of the unusual amino acid hypusine (N **epsilon** -(4-amino-2-hydroxybutyl) **lysine**). Evidence that hypusine is implicated in cell growth prompted this study of the cellular effects of these inhibitors. In Chinese hamster ovary (CHO) cells, inhibition of hypusine biosynthesis followed by progressive arrest in cellular proliferation was observed with both N-mono- and N,N'-bisguanyl derivatives of 1,6-diaminohexane, 1,7-diaminoheptane, and 1,8-diaminooctane. Cells treated with these compounds showed no significant change in polyamine distribution, suggesting that the observed growth inhibition is not mediated through an interference with polyamine metabolism. N1-guanyl-1,7-diaminoheptane, the most potent inhibitor of deoxyhypusine synthase both in vitro and in cells, exhibited the highest antiproliferative activity toward CHO cells. No early **cytotoxic** effects were observed with this inhibitor, and its antiproliferative activity appeared to be reversible. Transport studies showed that N1-guanyl-1,7-diaminoheptane is actively taken up by the polyamine transport system. Mutant CHO cells defective in polyamine transport were found to be resistant to growth inhibition by this compound. The findings suggest that the antiproliferative effect of N1-guanyl-1,7-diaminoheptane is exerted intracellularly through inhibition of hypusine synthesis.

10/9/21 (Item 4 from file: 155)

06329384 89345654 PMID: 2548206

Highly potent metallopeptide analogues of luteinizing hormone-releasing hormone.

Bajusz S; Janaky T; Csernus V J; Bokser L; Fekete M; Srkalovic G; Redding T W; Schally A V

Endocrine Polypeptide and Cancer Institute, Veterans Administration Medical Center, New Orleans, LA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Aug 1989, 86 (16) p6313-7, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: CA40003; CA; NCI; CA40004; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

Metal complexes related to the **cytotoxic** complexes cisplatin [cis-diamminedichloroplatinum(II)] and transbis(salicylaldoximato)copper(II) were incorporated into suitably modified luteinizing hormone-releasing hormone (LH-RH) analogues containing D- **lysine** at position 6. Some of the metallopeptides thus obtained proved to be highly active LH-RH agonists or antagonists. For instance, SB-40, a PtCl2-containing metallopeptide in which platinum is coordinated to an N **epsilon** -(DL-2,3-diaminopropionyl)-D- **lysine** residue [D-Lys(DL-A2pr] at position 6, showed 50 times higher LH-releasing potency than the native hormone. SB-95, [Ac-D-Nal(2)1,D-Phe(pCl)2, D-Pal(3)2, Arg5,D-Lys[DL-A2pr(Sal2Cu)]6,D-Ala10]LH-RH, where Nal(2) is 3-(2-naphthyl)alanine, Pal(3) is 3-(3-pyridyl)alanine, and copper(II) is coordinated to the salicylideneimino moieties resulting from condensation of salicylaldehyde

with D-Lys(DL-A2pr)6, caused 100% inhibition of ovulation at a dose of 3 micrograms in rats. Most metallopeptide analogues of LH-RH showed high affinities for the membrane receptors of rat pituitary and human breast cancer cells. Some of these metallopeptides had **cytotoxic** activity against human breast cancer and prostate cancer cell lines in vitro (this will be the subject of a separate paper on cytotoxicity evaluation). Such cytostatic metallopeptides could be envisioned as targeted chemotherapeutic agents in cancers that contain receptors for LH-RH-like **peptides** .

09/851,422

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